

REMARKS

Applicants have read and considered the Office Action dated November 15, 2004 and the references cited therein. Claims 1, 2, 9-11, 13-15, and 26 have now been amended. Claims 22-25 and 33-34 were previously cancelled. Claims 1-21, 26-32, and 35-41 are currently pending.

In the Office Action, claims 9 and 13-15 were rejected under 35 U.S.C. §112 as being indefinite. Errors were noted in those claims. Claims 9 and 13-15 have now been amended to correct the errors. Applicants assert that the rejections are traversed.

Claims 17-21, 35, and 36 were allowed. Applicants thank the Examiner for the allowance of these claims.

Claims 1-16, 26-32, and 37-41 were rejected as being unpatentable over the combined teachings of *Spaink*, *Stacey et al.*, *Stokkermans et al.*, *Schlaman et al.*, and *Röhrig et al.* Applicants assert that even if all of the references are combined, the combination neither teaches nor suggests the present invention. Moreover, it is impermissible to use the present invention as a roadmap for selecting and combining prior art references. See *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). The Federal Circuit has held that "the invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." See *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 USPQ 543 (Fed. Cir. 1985). Applicants assert that without impermissible hindsight reconstruction, the present invention cannot be viewed as obvious in light of the collection of prior art references.

In the present application, the Office Action appears to utilize hindsight reconstruction in combining a large number of references that do not teach or suggest combination with the other references. Moreover, the cited references do not teach or suggest the particular combination of steps of the present invention. None of the cited references either alone or in combination teach or suggest the present invention to one of ordinary skill in the art. Arriving at the presently recited invention requires further ingenuity relating to the effect of LCO's germination in emergence in either legumes or non-legumes or to the effect of LCOs in plant growth in non-legumes. The Action states that "one of ordinary skill in the art of photohormones (sic) would be motivated to combine these references because they disclose the utility of LCOs as

phytohormones and investigate their applicability beyond the effects on leguminous roots on which their effects were first noted." The Action states that "it would have been *prima facie* obvious to the ordinary artisan at the time the invention was made to have applied LCOs to both leguminous and nonleguminous plants because the prior art teaches that they were known phytohormones with activities directed to both classes of plants." The Action finally states that "the prior art teaches the application of LCOs, or rhizobial species which produce LCOs, to seedlings or plants; it is inconsequential what the results of such applications would be, or whether such results were noted in the prior art." Applicants respectfully disagree with these contentions and the rejection, as the rejection is only based on a collection of prior art references without motivation in any of the references to combine with one another. Moreover, the references do not lead one of ordinary skill in the art to arrive at the present invention without further invention.

Applicants assert that one of the references should be withdrawn as a basis for rejection. Applicants assert as Exhibit A an article from the magazine Science showing that the *Röhrig* reference is not applicable prior art as the results were not reproducible and the paper has been discredited and retracted. Applicants assert that one of ordinary skill in the art would not look to a paper has been revealed to be scientifically false for motivation to combine with other references, and Applicants assert that the rejection should be withdrawn.

Moreover, none of the prior art teaches or suggests the method of the present invention. The *Spaink*, *Stacey et al.*, and *Schlaman et al.* references teach that LCOs can act as a signal compound and as a plant hormone, but only in the context of legume-rhizobia nitrogen fixation symbiosis. This is also true of the relevant material in *Stokkermans et al.* These references teach signaling from the bacterium to the legume root in the context of root nodule initiation and development. The signal and hormonal effects of the LCOs are restricted in these cases to events associated with symbiotic infection and development of related structures. The stimulation of flavonoid and isoflavonoid production is typical of symbiotic and pathogenic infections, as is alkalization of growth media. Induction of genes relates only to the formation of root nodules and morphogenic activity relates to the triggering of nodule meristems and nodules themselves. All these references and their teachings are narrowly confined to nodule symbiosis, with no indication or suggestion of activity outside this system. There is no teaching or suggestion of

emergence or germination as recited in the claims of the present invention and no motivation to one of ordinary skill in such a narrow field to look to the field of the present invention. It is impermissible to use hindsight in combining references to extrapolate from these understandings the present invention. Such a leap requires invention; if such an invention is required, then an obviousness rejection is not proper.

Turning to *Stokkermans et al.*, the reference does not mention non-legumes, only artificial systems including cell cultures and somatic embryos forming in tissue culture systems. There is no teaching or suggestion that such application would lead to similar findings in intact plant systems and no motivation for combination with the other cited references. Moreover, in the case of embryos, the material contained a mutation that did not allow development of embryo development to go ahead. Such findings would actually teach away from the present invention and would suggest to one of ordinary skill in the art that the process and methods of the present invention would be stifled by such a method. Moreover, in the case of seed germination, as the embryos are already formed and do not carry a mutation, they do not require materials be added to them. Although added material might stimulate or accelerate germination, one could not extrapolate from the reference that with material missing because of mutation, one would arrive at the present invention. Furthermore, applying the teachings from a developing embryo to possible effects on a fully developed embryo is not obvious to one of ordinary skill in the art. Regarding alkalization, one of ordinary skill in the art could not extrapolate an effect that is not growth related on a suspension of cells outside the normal regulatory network of hormones and signals that coordinate normal plant growth and development, and then apply to the orchestrated development of an intact seedling going through the standard development steps with all the tissues of its various organs moving through growth and development. Such a leap requires invention by one of ordinary skill in the art. Applicants assert that the growth that can be promoted in a culture is not obviously applicable to the real world. Applicants further note that explanted tissue performs substantially differently in vitro based on various factors and that the present invention is directed to a substantially different environment with different conditions.

In summary, Applicants assert that the combination of the prior art references does not teach or suggest the present invention without use of hindsight reconstruction and requires a leap forward by one of ordinary skill in the art. The prior art teaches only the application of LCOs or

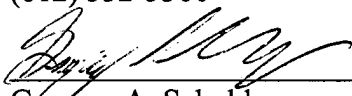
rhizobial species that produce LCOs to seedlings or plants. One of ordinary skill in the art would not be lead directly, without exercise of further inventive ingenuity and undue experimentation, to the present invention, which is directed to the use of LCOs in plant emergence and germination. Applicants respectfully disagree with the Examiner's assertion that what the results of such applications would be are inconsequential or whether such results would guide one of ordinary skill in the art. These results do not lead one of ordinary skill in the art to the present invention. Therefore, the prior art references, or any combination thereof, would not motivate one of ordinary skill in the art to combine the art, and one of ordinary skill in the art would not logically investigate the applicability of LCOs to plant emergence and germination, whether it was leguminous or non-leguminous without further invention.

A speedy and favorable action merits is hereby solicited. If the Examiner feels that a telephone interview may be helpful in this matter, please contact Applicants' representative at 612.336.4728.

Respectfully submitted,

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• Table of Contents •

PLANT SCIENCE:

Data in Key Papers Cannot Be Reproduced

Michael Balter

New findings, published last week, appear to confirm suspicions that several key papers in a hot area of plant development were fatally compromised by scientific fraud. The results, published in the March issue of *Plant Journal*, stem from an investigation at the Max Planck Institute for Plant Breeding Research in Cologne, Germany, which concluded last year that a laboratory technician falsified experiments forming the basis of 10 publications going back to 1992. The technician, Inge Czaja, and the leader of the group in which she worked, Richard Walden, resigned in early 1998 in the wake of the scandal, although Walden has never been accused of participating in the fraud.

In the *Plant Journal* article, a team of researchers at the Cologne institute, along with colleagues from other European labs, report on their attempts to repeat key experiments in eight papers published in *Science*, *EMBO Journal*, the *Proceedings of the National Academy of Sciences (PNAS)*, *Trends in Plant Science*, and *Plant Journal*. The authors could not reproduce the most central findings. Two other papers from the institute, which had originally appeared in *Nature* and *PNAS* in 1997, were retracted last year by most of their authors after their findings also could not be reproduced.

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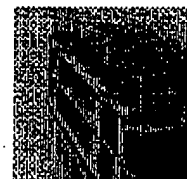
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COLOGNE INSTITUTE'S DISPUTED PAPERS

Irreproducible in the *Plant Journal* study:

Hayashi *et al.*, Activation of a plant gene by T-DNA tagging: Auxin-independent growth in vitro, *Science* 258, 1350 (1992).

Walden *et al.*, Auxin inducibility and developmental expression of *axl1*: A gene directing auxin-independent growth in tobacco protoplasts, *EMBO Journal* 13, 4729 (1994).

Röhrig *et al.*, Growth of tobacco protoplasts stimulated by synthetic lipo-chitoooligosaccharides, *Science* 269, 841 (1995).

Miklashevichs *et al.*, Do peptides control plant growth and development?, *Trends in Plant Science* 1, 411 (1996).

Van de Sande *et al.*, Modification of phytohormone response by a peptide encoded by *ENOD40* of legumes and a nonlegume, *Science* 273, 370 (1996).

Röhrig *et al.*, Convergent pathways for lipochitoooligosaccharide and auxin signaling in tobacco cells, *Proceedings of the National Academy of Sciences* 93, 13389 (1996).

Harling *et al.*, A plant cation-chloride co-transporter promoting cytokinin- and auxin-independent protoplast division, *EMBO Journal* 16, 5855 (1997).

Miklashevichs *et al.*, T-DNA tagging reveals a novel cDNA triggering cytokinin- and auxin-independent protoplast division, *Plant Journal* 12, 489 (1997).

Retracted last year:

Ichikawa *et al.*, Identification and role of adenylylcyclase in auxin signaling in higher plants, *Nature* 390, 698 (1997). [retracted: Ichikawa *et al.*, *Nature* 396, 390 (1998).]

John *et al.*, Lipochitoooligosaccharide-induced tobacco cells release a peptide as mediator of the glycolipid signal, *Proceedings of the National Academy of Sciences* 94, 10178 (1997). [retracted: John *et al.*, *PNAS* 95 (17), 10344a (1998).]

"I can no longer believe any parts of the data in any parts of the papers," says plant biologist Alan Jones of the University of North Carolina, Chapel Hill, who adds that the new findings will have "a negative effect on the field," because "major conclusions were drawn" from the papers. The lead author of the *Plant Journal* report, plant researcher Jeff Schell—who is head of the department in which the Walden group worked and a co-author on the disputed papers—agrees that all the major findings were "subject to falsification." Nevertheless, Jones, Schell, and other researchers stress that the basic techniques used in the research—which were pioneered by Walden and other colleagues—remain valid and are being enthusiastically used by other researchers. "This technology has been very influential," says plant molecular geneticist George Coupland of the John Innes Centre in Norwich, United Kingdom.

The affair dates from the early 1990s, when Walden and his co-workers pioneered a new way to study the actions of plant genes. The technique, called activation T-DNA tagging, creates mutations by inserting DNA from the soil bacterium *Agrobacterium tumefaciens*, which induces plant tumors, into the genome of plants they wish to study. They found that genes flanking this inserted foreign DNA were "overexpressed"; that is, they produced much higher levels of proteins than normal, allowing those genes and their protein products to be studied much more easily.

With this method, Walden and his co-workers began trying to decipher the poorly understood mechanisms of action of two plant hormones—auxin and cytokinin—that control plant cell division and growth. To do this, the team produced numerous mutants of tobacco plants which they thought were capable of growing independently of the presence of these two hormones. Using these mutants, the team isolated a number of genes, proteins, and other factors that appeared to stimulate plant growth "downstream" of the hormones—and thus were implicated in the hormones' mechanism of action.

It now appears, however, that these mutants were not capable of independent growth after all. The investigation carried out at the institute concluded that Czaja added plant growth factors to culture media used in the experiments and manipulated

the experiments to make it appear that cultured plant cells were capable of auxin- and cytokinin- independent cell division. (Czaja, who was also a co-author on the papers, declined to comment when contacted by *Science*.) Serious suspicions had been raised by early 1998, when researchers at the institute were unable to repeat results stemming from the technician's work. Walden and his co-workers began investigating and soon concluded that at least some of the results had been faked.

In March 1998, Walden informally let other plant researchers know that there were potential problems with the work, and the following month he, Schell, and another coworker published an initial warning about the data in *Trends in Plant Science*. Nevertheless, under strict new rules on scientific misconduct adopted by the Max Planck Society in November 1997, institute officials sought, and received, Walden's resignation. "There were ample signs that [Walden] did not exercise proper responsibility for his group," says Heinz Saedler, a co-director of the Cologne institute. (Walden, who now works at a research institute in the United Kingdom, told *Science* he preferred not to comment on the affair.)

Despite the dramatic findings in this month's *Plant Journal* report, Schell says the group has no immediate plans to publish retractions of the eight papers in the journals in which they originally appeared. "This article is about the only thing we were planning to do. The main thing is to get our science going again." On the other hand, Schell adds, if the journals themselves asked for retractions, "I would consider it very seriously." But some editors of the journals involved say they believe the co-authors should submit letters stating that the results could not be reproduced. John Tooze, co-executive editor of *EMBO Journal*, says that although the journal has no hard-and-fast policy about retractions, it would be "common sense" for the authors to contact the journals involved. "A statement in each of the journals from the authors would be an appropriate thing to do," he says. And Floyd Bloom, editor-in-chief of *Science*—where three of the eight papers appeared—says that "we would have expected Dr. Schell or his institution to contact us when the results that had been published in *Science* were conclusively identified as suspect. We will be discussing the possible need for retractions of the papers that Dr. Schell and his collaborators published in *Science* with him, and will act accordingly."

Jones says that, in retrospect, flaws in some of these papers might have been spotted with closer review. For example, in the *Plant Journal* study the researchers used a second assay technique—incorporation of the DNA building block thymidine into plant cells—in addition to a cell-counting method used in the original work to determine whether cell division had occurred. "In hindsight, why wasn't the thymidine incorporation done originally; why didn't the reviewers call for that?" Jones asks. On the other hand, he says, "hindsight isn't fair. ... When the papers came out I was extremely enthusiastic."

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